PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HSM-CHL-TAM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 02/00244	26.12.2002	26.12.2002

International Patent Classification (IPC) or both national classification and IPC

C07C303/40

Applicant

CADILA HEALTHCARE LIMITED et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of two sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.07.2004	31.03.2005

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 02/00244

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-11 as originally filed

Claims, Numbers

1-11 received on 06.12.2004 with letter of 04.12.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III ----------

Independent claim 11 relates to a process whereby the target compound "*is prepared in two step synthesis as shown in scheme 2*". Such a reference to the description is only allowable under exceptional circumstances, i.e. where absolutely necessary, which is, however, not the case here, see PCT Rule 6.2 (a) and the PCT Guidelines PCT/GL/ISPE/1 page 38, item 5.10.
Moreover, claim 11 as it stands does not indicate which technical features are actually claimed.

Re Item V ----------

Claim 1 relates to a process for the manufacture of optically pure (R) or (S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide by resolving the (R,S)-racemate via diastereomeric salt formation with D- or L-tartaric acid.

Present claim 1 is - at least partially - unclear having regard to terms such as " ... *solvents of the kind such as herein described*" and "... *base of the kind such as herein before described*" since there is no description of said features in the claim.
Moreover, the passage in claim 1 reading "*by using a suitable diastereomeric salts (...) whose differential solubility properties exploited in a suitable solvent system at a suitable temperature range*" merely indicates in quite general terms the (basically known) resolution principle to be employed.

Novelty of the subject-matter claimed can be acknowledged since none of the documents cited in the International Search Reports discloses a process as described in present claims 1 (Art. 33(2) PCT) .

The optical resolution of racemic mixtures of optically active (enantiomeric) compounds having functional groups which can react with a suitable optical active reagents, e.g. an optical active acid such as D- or L-tartaric acid, to give the corresponding the diastereomeric salts is a possibility which is basically known in the art (see, for example, D2, page 1565, col. 1, lines 13-30, and D3). It is also well known and evident to the skilled person that the separation of the diastereomeric salts so obtained is possible due to the different physicochemical properties of the diastereomers (e.g. the different solubility of the

diastereomeric forms) and that the efficiency of the separation, of course, strongly depends on the proper choice of a suitable solvent or solvent system (cf. e.g. D2: solvent is ethanol; D3: solvent system is water-alcohol), when fractional crystallization, the most common method for the separation of diastereomers, is used.
The particular choice of a suitable solvent (or solvent mixture) and suitable temperatures for efficiently separating a mixture of particular diastereomeric salts having a particular chemical structure is considered to be a routine operation for the skilled person, not requiring an inventive activity (Art. 33(3) PCT).
The method claimed is thus considered to be merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the underlying technical problem (=resolution of (R,S)-5-(2-aminopropyl)-2-methoxy-benzene sulfonamide to give the corresponding R(-) and S(+) enantiomer).
Dependent claims 2-10 do not appear to contain any features which, in combination with the features of any claim to which they refer, add inventive matter, i.e. relate to features or embodiments which require an inventive activity.

The subject-matter claimed meets the requirements of Art. 33(4) PCT (industrial applicability).

Claims.

1. A process for manufacture of optically pure (R) or (S) -5-(2-aminopropyl)-2-methoxybenzenesulfonamide by using a suitable diasteromeric salts of (R, S) -5-(2-aminopropyl)-2-methoxybenzenesulfonamide whose differential solubility properties exploited in a suitable solvent system at a suitable temperature range obtains desired optically phase (R)-(-)-5-(2-aminopropyl) -2 melhoxtbenzenSulfonamide, said process comprising resolving (R, S)- 5-(2-aminopropyl)-2-methoxybenzenesulfonamide with D-or L-tartaric acid to form a mixture of diastereomeric salts, separating the diastereomeric salts in any known manner in the presence of inert organic solvents of the kind such as herein described and contacting the individual salts so separated with base of the kind such as herein before described to provide said R -(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide or S-(+)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide, wherein the ratio of the polar solvent to alcoholic solvent varies from 5 to 20% (v/v), and said said resolution is carried out in a temperature range of 50-70°C.

2. A process as claimed in claim 1 wherein the ratio of (R, S)- 5-(2-aminopropyl)-2-methoxybenzenesulfonamide to tartaric acid is in the range of 1:1 to 1:1.1.

3. A process as claimed in claim 1 or 2 wherein resolution is carried out in two stages in presence of a solvent system consisting of alcoholic solvents coupled with varying ratios of polar solvents such as amidic solvents like dimethylformamide, N-methyl-2-pyrrolidone or dimethylsulfoxide or water.

4. A process as claimed in claim 1 wherein said resolution is preferably carried out at a temperature in the range of 60-65°C.

5. A process as claimed in any of the preceding claims wherein the said reaction time is between 4 to 26 hrs.

6. A process as claimed in any of the preceding claims wherein the inert organic solvent used for separating the diastereomeric salts to individual salts is selected from the group consisting of one or more of methanol, ethyl alcohol, propyl alcohol, water, dimethylformamide, N-methyl-2-pyrrolidone, dimethylsulfoxide.

7. A process as claimed in any of the preceding claim wherein the base is sodium hydroxide & the pH for isolation of free base is 9.5-10.

8. A process as claimed in any one of the preceding claims, whereby melting point of tartarate salt of more than 188^{0}C is obtained after first stage operations.

9. A process as claimed in any one of the preceding claims, whereby an optically purity of more than >99.5% is obtained after second stage operations.

10. A process as claimed in any one of the preceding claims, wherein 5-(2-aminopropyl)-2-methoxybenzenesulfonamide is obtained in more than 90% optical purity from the second stage mother liquor.

11. A process whereby racemic (R,S) 5-(2-aminopropyl)-2-methoxybenzenesulfonamide is prepared in two step synthesis as shown in scheme: 2 from 5-acetonyl-2- methoxybenzenesulfonamide.